Smokeless tobacco and tobacco-related nitrosamines

Vincent Cogliano, Kurt Straif, Robert Baan, Yann Grosse, Béatrice Secretan, Fatiha El Ghissassi
WHO International Agency for Research on Cancer

Upcoming meetings

Dec 16–18, 2004	Planning for series of monographs on air pollution
Feb 15–22, 2005	Human papillomaviruses
June 7–14, 2005	Hormone therapy

19 scientists from seven countries (see panel) met at the International Agency for Research on Cancer (IARC; Lyon, France) in October, 2004, to assess the carcinogenicity of smokeless tobacco and related nitrosamines.[1] Many types of smokeless tobacco are marketed for oral or nasal use, and all contain different amounts of nicotine and nitrosamines. Hundreds of millions of people are addicted to smokeless tobacco, and use by young people is increasing in many countries. Some health scientists attribute the low prevalence of smoking in Sweden to use of moist snuff, but the IARC Working Group found that the evidence does not support such claims.

A case-control study[2] in the USA strongly associated oral cancer with use of moist snuff by non-smokers who did not drink alcohol. The researchers reported a dose-response relation between duration of use and risk of cancers of the gum and buccal mucosa. Four case-control studies from India and Pakistan reported increased risks of 2–15 times in people who chewed tobacco, after investigation for potential confounding factors of betel-quid chewing, smoking, and alcohol consumption. A Swedish case-control study found no significant association between use of moist snuff and overall risk of head and neck cancer; however snuff use in never smokers was associated with almost a five-times increased risk of head and neck cancer. Another Swedish case-control study found no association between use of moist snuff and oral cancer, but some notable subgroups (including never smokers and people with lip cancer) had increased relative risks of borderline significance. A US cohort study found a non-significant increased risk of oral cancer in never smokers who used smokeless tobacco.

In one US case-control study,[3] incidence of pancreatic cancer was significantly higher in users of smokeless tobacco who were non-smokers. Another US case-control study found a greater risk in heavy users of smokeless tobacco who had never smoked. A cohort study[4] of men in Norway found an excess risk of pancreatic cancer in ever users of smokeless tobacco, after controlling for smoking, and a cohort study in the USA found an excess risk of borderline significance in ever users, after adjustment for smoking and alcohol consumption.

Two studies in which rats were repeatedly exposed to moist snuff in a surgically created oral canal found a significantly increased incidence of cancers of the oral and nasal cavities, forestomach, and lip.

Overall, there is sufficient evidence that smokeless tobacco causes oral cancer and pancreatic cancer in humans, and sufficient evidence of carcinogenicity from animal studies. The Working Group concluded that smokeless tobacco is "carcinogenic to humans".

Tobacco-specific nitrosamines such as *N*′-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), *N*′-nitrosoanatabine (NAT), and *N*′-nitrosoanabasine (NAB), form by the nitrosation of nicotine and other tobacco alkaloids. Substantial quantities form during the curing and processing of tobacco, as well as during smoking.

Many studies in animals have showed that different routes of exposure to NNN and NNK cause benign and malignant tumours of the nasal cavity, lung, and trachea.[5] Furthermore, NNK causes pancreatic and liver tumours, and NNN causes oesophageal tumours. Results of epidemiological studies of users of smoked and smokeless tobacco plausibly associate NNN and NNK with cancer in humans, but these studies cannot exclude confounding by many other carcinogens present in tobacco and tobacco smoke.

The Working Group concluded that exposure to NNN and NNK is "carcinogenic to humans", on the basis of sufficient evidence from animals and strong mechanistic evidence in exposed humans. NNN and NNK are the most abundant strong carcinogens in smokeless tobacco; uptake and metabolic activation in smokeless-tobacco users have been clearly observed. In rats, combined application of NNN and NNK induced oral tumours, consistent with induction of oral tumours by smokeless tobacco. One of the mechanisms of carcinogenicity is cytochrome-P450-mediated α-hydroxylation, which leads to DNA adducts and haemoglobin adducts, commonly detected in tobacco.

IARC Monograph Working Group

JM Rice—*Chair* (USA), SS Hecht—*Co-chair* (USA), J Nair, UJ Nair (Germany); RA Bhisey, PC Gupta, R Rajhan, DN Sinha (India); D Zaridze (Russian Federation); AM Idris (Saudi Arabia); A Ahlbom (Sweden); S Warnakulasuriya (UK); S Asma, MV Djordjevic, J Jinot, W Pickworth, G Stoner, SL Tomar, DM Winn (USA).

Conflict of interest

The authors and the Working Group declare no conflicts of interest.

References

1 IARC monographs on the evaluation of carcinogenic risks to humans. Volume 89: smokeless tobacco and some tobacco-specific nitrosamines. Lyon: IARC Press (in press).
2 Winn DM, Blot WJ, Shy CM, et al. Snuff dipping and oral cancer among women in the southern United States. *N Engl J Med* 1981; **304:** 745–49.
3 Muscat JE, Stellman SD, Hoffmann D, Wynder EL. Smoking and pancreatic cancer in men and women. *Cancer Epidemiol Biomarkers Prev* 1997; **6:** 15–19.
4 Boffetta P, Aagnes B, Weiderpass E, Andersen A. Smokeless tobacco use and risk of cancer of the pancreas and other organs. *Int J Cancer* (in press).
5 Hecht SS. Biochemistry, biology, and carcinogenicity of tobacco-specific N-nitrosamines. *Chem Res Toxicol* 1998; **11:** 559–603.